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PCT/GB 2005 / 0 0 1 0 3 1

INVESTOR IN PEOPLE

The Patent Office
Concept House
Cardiff Road
Newport
South Wales
NP10 8QQ

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Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

17 MAR 2004

The Patent Office

Cardiff Road
Newport
South Wales
NP10 8QQ

1. Your reference — REP07705GB

2. Patent application number *(The Patent Office will fill this part in)* — 0406016.6

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

Arakis Ltd.
Chesterford Research Park
Little Chesterford
Saffron Walden
Essex CB10 1XL

Patents ADP number *(if you know it)*

If the applicant is a corporate body, give the country/state of its incorporation — United Kingdom

8306128001

4. Title of the invention — The treatment of inflammatory disorders

5. Name of your agent *(if you have one)* — Gill Jennings & Every

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

Broadgate House
7 Eldon Street
London
EC2M 7LH

Patents ADP number *(if you know it)* — 745002

6. Priority: Complete this section if you are declaring priority from one or more earlier patent applications, filed in the last 12 months.

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. Divisionals, etc: Complete this section only if this application is a divisional application or resulted from an entitlement dispute (see note f)

Number of earlier UK application	Date of filing *(day / month / year)*

8. Is a Patents Form 7/77 (Statement of inventorship and of right to grant of a patent) required in support of this request? — YES

Answer YES if:

a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is not named as an applicant, or
c) any named applicant is a corporate body.

Otherwise answer NO (See note d)

9 Accompanying documents: A patent application must include a description of the invention. Not counting duplicates, please enter the number of pages of each item accompanying this form:

Continuation sheets of this form	
Description	5
Claim(s)	2
Abstract	
Drawing(s)	

10. If you are also filing any of the following, state how many against each item.

Priority documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent (Patents Form 7/77)	
Request for a preliminary examination and search (Patents Form 9/77)	
Request for a substantive examination (Patents Form 10/77)	NO
Any other documents (please specify)	

11. I/We request the grant of a patent on the basis of this application.

For the applicant
Gill Jennings & Every

Signature

Date 17 March 2004

12. Name, daytime telephone number and e-mail address, if any, of person to contact in the United Kingdom

PERRY, Robert Edward
020 7377 1377

Warning

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Notes

a) If you need help to fill in this form or you have any questions, please contact the Patent Office on 08459 500505.

b) Write your answers in capital letters using black ink or you may type them.

c) If there is not enough space for all the relevant details on any part of this form, please continue on a separate sheet of paper and write "see continuation sheet" in the relevant part(s). Any continuation sheet should be attached to this form.

d) If you have answered YES in part 8, a Patents Form 7/77 will need to be filed.

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f) Part 7 should only be completed when a divisional application is being made under section 15(4), or when an application is being made under section 8(3), 12(6) or 37(4) following an entitlement dispute. By completing part 7 you are requesting that this application takes the same filing date as an earlier UK application. If you want the new application to have the same priority date(s) as the earlier UK application, you should also complete part 6 with the priority details.

The treatment of inflammatory disorders

Field of the invention

This invention relates to the treatment of inflammatory disorders

Background

Inflammatory diseases remain poorly treated, including many autoimmune diseases, certain IgE mediated (Type I) hypersensitivity reactions, chronic inflammatory disease and skin inflammation. In these patients treatment regimes are often not wholly effective, or are halted due to excessive side effects, allowing the disease to progress. Consequently, there is a need for drugs which are effective in treating these immune mediated inflammatory conditions, but with substantially fewer side effects.

Immune driven inflammatory events are a significant cause of many chronic inflammatory diseases where prolonged inflammation causes tissue destruction and results in extensive damage and eventual failure of the affected organ. The cause of these diseases is unknown, so are often called autoimmune, as they appear to originate from an individual's immune system turning on itself. Conditions include those involving multiple organs, such as systemic lupus erythematosus (SLE) and scleroderma. Other types of autoimmune disease can involve specific tissues or organs such as the musculoskeletal tissue (rheumatoid arthritis, ankylosing spondylitis), gastro-intestinal tract, (Crohn's disease and ulcerative colitis), the central nervous system (Alzheimers, Multiple sclerosis, motor neurone disease, Parkinson's disease and chronic fatigue syndrome), pancreatic beta cells (insulin dependent diabetes mellitus), the adrenal gland (Addison's diseae), the kidney (Goodpasture's syndrome, IgA nephropathy, interstitial nephritis) exocrine glands (Sjogrens syndrome and autoimmune pancreatitis) and skin (psoriasis and atopic dermatitis).

In addition, there are chronic inflammatory diseases whose aetiology is more or less known but whose inflammation

is also chronic and unremitting. These also exhibit massive tissue/organ destruction and include conditions such as osteoarthritis, periodontal disease, diabetic nephropathy, chronic obstructive pulmonary disease, artherosclerosis, graft versus host disease, chronic pelvic inflammatory disease, endometriosis, chronic hepatitis and tuberculosis. In these diseases the tissue destruction often damages organ function, resulting in progressive reductions in quality of life and organ failure. These conditions are a major cause of illness in the developing world and poorly treated by current therapies.

IgE mediated (Type I) hypersensitivity reactions result from an inappropriate response to normally non-immunogenic antigens (e.g, pollen and dust-mites). Antigen presentation results in eosinophil infiltration, cytokine burst, inflammation and oedema. These conditions can be triggered by antigens such as mould, dust mites, grass and tree pollenm and result in conditions such as rhinitis, asthma, anaphylaxis and dermatitis.

Inflammation of skin structures (dermatitis) is a common set of conditions which include; actinic keratosis, acne rosacea, acne vulgaris, allergic contact dermatitis, angioedema, atopic dermatitis, bullous pemiphigoid, cutaneous drug reactions, erythema multiforme, lupus erythrametosus, photodermatitis, psoriasis, psoriatic arthritis, scleroderma and urticaria. These diseases are treated using a wide array of therapies, many of which have very severe side effects.

Current disease modifying treatments (if any), for immune driven conditions, include neutralising antibodies, cytotoxics, corticosteriods, immunosuppressants, antihistamines and antimuscarinics. These treatments are often associated with inconvenient routes of administration and severe side effects leading to compliance issues. Moreover certain drug classes are only effective for certain types of inflammatory diseases; e.g. antihistamines for rhinitis.

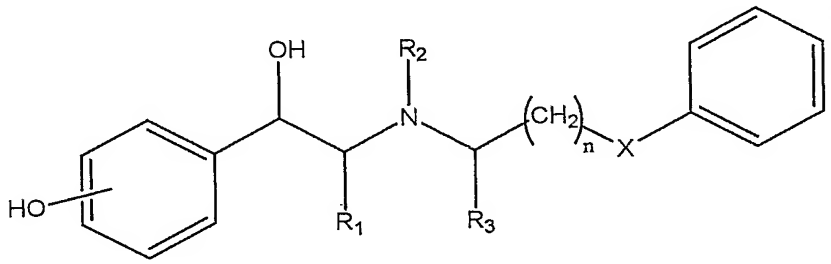
Phenyl substituted beta-amino alcohols (I) are known to have antihypertensive, vasodilator, sympathomimetic, bronchodilator or cardiostimulant activity through agonism and antagonism at alpha and beta adrenoceptors.

Summary of invention

Surprisingly it has been found that phenyl substituted beta-amino alcohols (I) are inhibitors of cytokines and possess anti-inflammatory properties. According to the present invention an inflammatory condition as previously described is treated by the use of (I).

Description of Preferred Embodiments

Phenyl substituted beta-amino alcohols refer to compounds of general formula (I)



(I)

Wherein:

R_1 may be H or Me

R_2 may be H or alkyl and can be part of a ring with R_3

R_3 may be H or Me or CH_2 (when forming part of a ring with R_2)

n=0-2

X may be CH_2 or O

The two phenyl groups may be optionally substituted with OH, OMe, halogen, NHCHO, $NHSO_2Me$, $CONH_2$, SOMe

It is understood that the invention refers to salts, e.g. the hydrochloride, metabolites and pro-drugs thereof, as well as any diastereomers and enantiomers of (I).

Compounds of formula (I) include bufeniode, butopamine, denopamine, fenoterol, formoterol, ifenprodil, isoxuprine,

labetalol, medroxalol, mesuprine, nylidrin, protokylol, ritodrine, salmefamol, sulfinalol.

According to the invention compounds of formula (I) are used to treat inflammatory diseases including, but not exclusive to, autoimmune diseases involving multiple organs, such as systemic lupus erythematosus (SLE) and scleroderma, specific tissues or organs such as the musculoskeletal tissue (rheumatoid arthritis, ankylosing spondylitis), gastro-intestinal tract, (Crohn's disease and ulcerative colitis), the central nervous system (Alzheimers, Multiple sclerosis, motor neurone disease, Parkinson's disease and chronic fatigue syndrome), pancreatic beta cells (insulin dependent diabetes mellitus), the adrenal gland (Addison's diseae), the kidney (Goodpasture's syndrome, IgA nephropathy, interstitial nephritis) exocrine glands (Sjogrens syndrome and autoimmune pancreatitis) and skin (psoriasis and atopic dermatitis), chronic inflammatory diseases such as osteoarthritis, periodontal disease, diabetic nephropathy, chronic obstructive pulmonary disease, artherosclerosis, graft versus host disease, chronic pelvic inflammatory disease, endometriosis, chronic hepatitis and tuberculosis, IgE mediated (Type I) hypersensitivities such as rhinitis, asthma, anaphylaxis and dermatitis. Dermatitis conditions include; actinic keratosis, acne rosacea, acne vulgaris, allergic contact dermatitis, angioedema, atopic dermatitis, bullous pemiphigoid, cutaneous drug reactions, erythema multiforme, lupus erythrametosus, photodermatitis, psoriasis, psoriatic arthritis, scleroderma and urticaria.

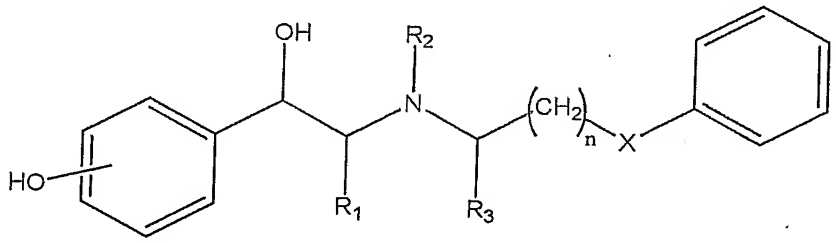
These compounds may be used according to the invention when the patient is also administered or in combination with another therapeutic agent selected from corticosteroids (examples including cortisol, cortisone, hydrocortisone, dihydrocortisone, fludrocortisone, prednisone, prednisolone, deflazacort, flunisolide, beconase, methylprednisolone, triamcinolone, betamethasone, and dexamethasone), disease modifying anti-rheumatic drugs (DMARDs) (examples including, azulfidine, aurothiomalate, bucillamine, chlorambucil,

cyclophosphamide, leflunomide, methotrexate, mizoribine, penicillamine and sulphasalazine), immunosuppressants (examples including azathioprine, cyclosporin, mycophenolate), COX inhibitors (examples including aceclofenac, acemetacin, alcofenac, alminoprofen, aloxipirin, amfenac, aminophenazone, antraphenine, aspirin, azapropazone, benorilate, benoxaprofen, benzydamine, butibufen, celecoxib, chlorthenoxacine, choline salicylate, chlometacin, dexketoprofen, diclofenac, diflunisal, emorfazone, epirizole, etodolac, feclobuzone, felbinac, fenbufen, fenclofenac, flurbiprofen, glafenine, hydroxylethyl salicylate, ibuprofen, indometacin, indoprofen, ketoprofen, ketorolac, lactyl phenetidin, loxoprofen, mefenamic acid, metamizole, mofebutazone, mofezolac, nabumetone, naproxen, nifenazone, oxametacin, phenacetin, pipebuzone, pranoprofen, propyphenazone, proquazone, rofecoxib, salicylamide, salsalate, sulindac, suprofen, tiaramide, tinoridine, tolfenamic acid, zomepirac) neutralising antibodies (examples including, etanercept and infliximab), antibiotics (examples including, doxycycline and minocycline).

Any suitable route of administration can be used. For example, any of oral, topical, parenteralocular, rectal, vaginal, inhalation, buccal, sublingual and intranasal delivery routes may be suitable. The dose of the active agent will depend on the nature and degree of the condition, the age and condition of the patient and other factors known to those skilled in the art. A typical dose is 10-100 mg given one to three times per day.

Claims

1. Use of a compound for the treatment or prevention of a condition associated with T-cell proliferation or that is mediated by pro-inflammatory cytokines, wherein the compound is of Formula I



(I)

Wherein:

R_1 may be H or Me

R_2 may be H or alkyl and can be part of a ring with R_3

R_3 may be H or Me or CH_2 (when forming part of a ring with R_2)

n=0-2

X may be CH_2 or O

Each benzene ring is optionally substituted with OH, OMe, halogen, NHCHO, $NHSO_2Me$, $CONH_2$ or SOMe.

2. Use according to claim 1 wherein the compound is selected from bufeniode, butopamine, denopamine, fenoterol, formoterol, ifenprodil, isoxuprine, labetalol, medroxalol, mesuprine, nylidrin, protokylol, ritodrine, salmefamol, sulfinalol.

3. Use according to claim 1 or 2 wherein the condition is a chronic degenerative disease such as rheumatoid arthritis, osteoarthritis or osteoporosis.

4. Use according to claim 1 or 2 wherein the condition is a chronic demyelinating disease such as multiple sclerosis.

5. Use according to claim 1 or 2 wherein the condition is a respiratory disease such as asthma or chronic obstructive pulmonary disease.

6. Use according to claim 1 or 2 wherein the condition is an inflammatory bowel disease (IBD) such as ulcerative colitis or Crohn's disease.

7. Use according to claim 1 or 2 wherein the condition is a dermatological condition such as psoriasis, scleroderma or atopic dermatitis.

8. Use according to claim 1 or 2 wherein the condition is a dental disease such as periodontal disease or gingivitis.

9. Use according to claim 1 or 2, wherein the condition is diabetic nephropathy, lupus nephritis, IgA nephropathy or glomerulonephritis.

10. Use according to claim 1 or 2 wherein the condition is systemic lupus erythematosus (SLE).

11. Use according to claim 1 or 2 wherein the condition is graft vs host disease.

12. Use according to any preceding claim wherein the patient is also administered another therapeutic agent selected from corticosteroids, cytotoxics, antibiotics, immunosupressants and COX inhibitors.

13. Use according to claim 12 wherein compound (I) and said another agent are provided in combination.